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Docket No.: PF-0356-4 CPA

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1652

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By: _____ Printed: Lyza Finuliar

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Lal et al.

Title:	HUMAN REGULATORY MOLECULES		
Serial No.:	09/840,787	Filing Date:	April 23, 2001
Examiner:	Slobodyansky, E.	Group Art Unit:	1652

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed **May 30, 2003**, and received by the USPTO on **June 2, 2003**, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $ **320.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 2-14 and 21 of the above-identified application.

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(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc., (now Incyte Corporation, formerly known as Incyte Genomics, Inc.) (Reel 9106, Frame 0593) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 2-14 and 21
Claims allowed:	(none)
Claims canceled:	Claims 1 and 15-20
Claims withdrawn:	(none)
Claims on Appeal:	Claims 2-14 and 15-20 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to polynucleotides encoding a human regulatory molecule, HRM-19. HRM-19 is identified in the specification as a member of the class of mitochondrial carrier proteins, whose biological functions include transport of ions and charged metabolites between the cytosol and the mitochondrial matrix. HRM-19 is 351 amino acids in length and shares sequence homology with *C. elegans* C16C10 (g577542) (specification, page 18, lines 25-28; Table 1, page 11). In addition, HRM-19 contains a mitochondrial carrier motif, P_{31}LDVVKVRL (specification, page 18, lines 26-27).

Furthermore, Northern analysis shows the expression of HRM-19-encoding sequences in cDNA libraries associated with cell proliferation, cancer, and the immune response (page 18, line 28). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the screening and diagnosis of cancer, none of which require knowledge of how the

polypeptide encoded by the claimed polynucleotides actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

(6) ISSUES

1. Whether claims 2-14 and 21 directed to human polynucleotide sequences encoding HRM-19 meet the utility requirement of 35 U.S.C. §101.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

(8) APPELLANTS' ARGUMENTS

Claims 2-14 and 21 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that "the main utility of the polypeptide and nucleic acid is to carry out further research to identify the biological function and possible diseases associated with said function. Substantial utility defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities" (Final Office Action, page 7). **The rejection of claims 2-14 and 21 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.**

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in humans. The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of mitochondrial carrier proteins, whose biological functions include transport of ions and charged metabolites between the cytosol and the mitochondrial matrix. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Appellants have previously submitted (with the Preliminary Amendment filed December 9, 2002) the Declaration of Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Final Office Action with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on September 23, 1997] that cDNA microarrays that contained the SEQ ID NO:19-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity.

The Final Office Action does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Final Office Action contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression"

such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Use of the claimed polynucleotides for diagnosis of conditions or diseases characterized by expression of HRM-19, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration

submitted with the Preliminary Amendment mailed December 9, 2002. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of polynucleotides encoding HRM-19 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses have been explained in detail in the Bedilion Declaration submitted with the Preliminary Amendment mailed December 9, 2002, the substance of which is not rebutted by the Final Office Action. There is no doubt that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis.

The Final Office Action asserts that the claimed polynucleotides encoding SEQ ID NO:19 do not meet the requirements described in the specification for polynucleotides used in a microarray, because the claimed sequences allegedly are not "specific to a gene of interest" or common to a particular cell or tissue type or disease state (Final Office Action, page 4). To the contrary, Appellants respectfully point out that the claimed sequences encoding SEQ ID NO:19 are certainly "specific" to a gene of interest, since the claimed polynucleotides are not mere fragments that could be portions of many genes, but are full-length sequences that encode one specific protein, SEQ ID NO:19. The Patent Examiner may hold the opinion that SEQ ID NO:19 is not "of interest," but as discussed in greater detail below this opinion is not supported by any evidence, and is in direct contradiction to the testimony of those of skill in the art, and the known literature. In addition, as discussed in greater detail in section II.D, although such an association is not required for utility, the claimed polynucleotides are specifically associated with a disease state, lung cancer. Thus the claimed invention is indeed a useful tool in cDNA microarrays, and that is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explained the many reasons why a person skilled in the art reading the Lal '750 application (the great-grandparent of the Lal '787 application) on September 23, 1997 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of

that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerned the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion stated that the 'Lal '750 specification would have led a person skilled in the art on September 23, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cell proliferative disorders [a] to conclude that a cDNA microarray that contained the SEQ ID NO:19-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:19-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on September 23, 1997] that a cDNA microarray that contained the SEQ ID NO:19-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-September 23, 1997 publications showing the state of the art on September 23, 1997 (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost four pages of text and seven subparts (a)-(g), he specifically stated that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on September 23, 1997 (and

[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Lal '750 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

for several years prior to September 23, 1997) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Lal '750 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Lal '750 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:19-encoding polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to September 23, 1997" (Bedilion Declaration, ¶ 15, item (g)). This, by itself, provides more than sufficient reason to compel the conclusion that the Lal '750 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

As described on pages 49-51 of the instant application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Final Office Action asserts that the above analogies are invalid because allegedly "the addition of a DNA encoding SEQ ID NO:19 to a microarray does not impart the utility if the microarray did not have one" (Final Office Action, page 9). While it is true that a microarray that did not contain the SEQ ID NO:19-encoding polynucleotides could be useful, "cDNA microarrays that contained the SEQ ID NO:19-encoding polynucleotides would be a **more useful** tool than cDNA microarrays that did not contain the polynucleotides" (Bedilion Declaration ¶ 15, emphasis added). There is no rule that states that an invention cannot be useful if it adds utility to an existing invention which also has utility -- in fact, the Patent Office regularly grants patents to improvements of well known devices and techniques.

In the Final Office Action the Patent Examiner agreed that whole genome arrays are useful (Final Office Action, page 7). Clearly, if a whole genome array has utility, the individual members of the array also have utility which they contribute to the array, since without any member of the array, the array is less complete, and thus less useful. Thus each individual sequence has a utility in creating arrays. Each of these individual members has a unique and specific utility in that it records the expression level of a unique gene.

Though Appellants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cell proliferative disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed in cells and tissues associated with cell proliferation, cancer, and the immune response (see the specification at p. 18, line 28), and expresses a protein that is a member of a class (mitochondrial carrier proteins) known to be associated with diseases such as cancer, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential cancer drug candidate or potential toxin with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(g)).

The Bedilion Declaration showed that a number of pre-September 23, 1997 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene

expression monitoring applications at the time the Lal '750 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Lal '750 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up– or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a

> xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999) (Reference No. 1, enclosed).

In a pre-September 23, 1997 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (Reference No. 2, enclosed) (emphasis added).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Dr. Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999) (Reference No. 3, enclosed); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000) (Reference No. 4, enclosed).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999) (Reference No. 5, enclosed). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See the email (Reference No. 6, enclosed) from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected

control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

The Final Office Action incorrectly asserts that "the specification lacks any mentioning of toxicology testing" (Final Office Action, pages 8-9). The Board's attention is respectfully directed to the specification at, for example, page 49, lines 15-19, wherein the specification discloses that HRM encoding sequences may be used "in developing and in monitoring the activities of therapeutic agents," which would include their potential toxic effects. The specification further discloses that assays which measure the expression of HRM "may be used to evaluate the efficacy of a particular therapeutic treatment regimen," (specification, page 48, lines 14-16) which would include checking for toxic side effects. Thus toxicology testing was not only well known in the art at the time of filing, but also disclosed in the specification as filed.

Appellants also respectfully point out that the Final Office Action refused to consider that the claimed polynucleotides are useful for measuring the toxicity of drug candidates which are targeted **not** to the claimed polynucleotides or the polypeptides they encode, but to **other genes or proteins**. This utility of the claimed polynucleotides does not require any knowledge of the biological function or disease association of the polypeptides they encode, and is a specific, substantial and credible utility.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The

implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Final Office Action failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections in the Final Office Action should be overturned regardless of their merit.

C. The fact that the claimed polynucleotide encodes a protein in the mitochondrial carrier protein family also demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, it is undisputed that the claimed polynucleotide encodes a protein having the sequence shown as SEQ ID NO:19 in the patent application and referred to as HRM-19 in that application. Appellants have demonstrated that HRM-19 is a member of the mitochondrial carrier protein family, and that the mitochondrial carrier family of proteins includes carriers involved in the transport of ions and charged metabolites between the cytosol and the mitochondrial matrix.

It is undisputed, and readily apparent from the patent application, that the polypeptide encoded for by the claimed polynucleotide shares more than 35% amino acid sequence identity over 351 amino acid residues with *C. elegans* C16C10 (g577542) (Lal '750 application, p. 18, lines 27-28; Table 1), a putative mitochondrial carrier protein. In addition, HRM-19 contains a mitochondrial carrier motif, P_{31}LDVVKVRL (Lal '750 application, p. 18, lines 26-27). This is more than enough homology to demonstrate a reasonable probability that the utility of the mitochondrial carrier protein family can be imputed to the claimed invention (through the polypeptide it encodes). The Examiner has previously asserted that "[i]n most cases, such a degree of homology does not allow the prediction of specific function" (Office Action mailed September 12, 2002, page 7). To the contrary, it is well-known that

the probability that two unrelated polypeptides share more than 30% sequence homology over 150 amino acid residues is exceedingly small. See Brenner et al., Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, 95 Proc. Natl. Acad. Sci., 6073 (1998) (Reference No. 7, enclosed). Given homology in excess of 30% over many more than 150 amino acid residues, the probability that the polypeptide encoded for by the claimed polynucleotide is related to the *C. elegans* mitochondrial carrier protein is, accordingly, very high.

The Final Office Action does not dispute any of the facts set forth in the previous paragraph. Neither does the Final Office Action dispute that, if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility.

The Examiner must accept the applicant's demonstration that the polypeptide encoded by the claimed invention is a member of the mitochondrial carrier protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Final Office Action has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Final Office Action provided any evidence that any member of the mitochondrial carrier protein family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention must be, like the other members of the mitochondrial carrier protein family, useful.

Instead, the Final Office Action asserts that "the present specification did not demonstrate the function of HRM-19 in mitochondria and, if it is a member of the class of mitochondrial carrier proteins, the specification did not demonstrate its substrate specificity" (Final Office Action, page 8). The Final Office Action also makes much of the disclosure in the Yu article (Yu et al., Overexpression of the human 2-oxogluatarate carrier lowers mitochondrial membrane potential in HEK-293 cells: contrast with the unique cold-induced mitochondrial carrier CGI-69, 353 Biochem J., 369 (2001) (Reference No. 8, enclosed)) that HRM-19 does not have the precise same function, uncoupling behavior, as some other known mitochondrial carrier proteins (Final Office Action, pages 11-12). Appellants respectfully

point out that the Yu article agrees with Appellants that the HRM-19 is a mitochondrial carrier with a probable role in supporting the enhanced ion and metabolic flux inherent to thermogenic brown adipose tissue (Yu, page 374, col. 2). Moreover, the Examiner is confusing, once again, function with use. These are not synonymous. Despite having different biological functions, mitochondrial carrier proteins can indeed have many common uses, such as toxicology controls. In any event, it does not matter that there may be more than one use for mitochondrial carrier proteins. The point for the purposes of the utility standard is that they are all indeed useful, which proves more than probable utility of the claimed invention.

D. The fact that the claimed polynucleotide is overexpressed in lung tumor tissue also demonstrates utility

The Final Office Action asserts that "[e]vidence of a differential expression might serve as a basis for the use of the claimed polynucleotide as a diagnostic for a disease," but that in the absence of "any correlation between the claimed polynucleotide with any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself" (Final Office Action, page 6). This is irrelevant. Appellants need not demonstrate whether the claimed polynucleotides are differentially expressed, only whether the claimed polynucleotides are useful. The claimed polynucleotides are useful (for example, as controls in toxicology testing) whether or not they are differentially expressed in any tissues or disease states.

While expressly not conceding that an association with specific diseases is necessary to demonstrate the utility of polynucleotides encoding HRM-19, Appellants respectfully point out the ample evidence indicating an association between HRM-19 expression and a specific disease, lung cancer. The Response to Office Action filed September 3, 2002 included the Declaration of Preeti Lal. In her Declaration, Dr. Lal discussed the differential expression of mRNA encoding the polypeptide in lung cancer as demonstrated in the microarray data shown in Exhibit D accompanying the Declaration. The Lal Declaration clearly demonstrates that the transcripts for HRM-19 were significantly, differentially, up-regulated (overexpressed) in lung tissue samples from cancer patients as compared to

matched normal samples from the same patient. Therefore, HRM-19, and the cDNA encoding it, are of diagnostic use in detecting lung cancers.

In her Declaration, Dr. Lal stated that she would present "evidence illustrating that HRM-19 and its encoding polynucleotide can be used in the detection of lung cancer. One way of demonstrating this utility is to show the expression profiles for transcripts that encode HRM-19. This analysis has been done for SEQ ID NO:68 employing microarray analysis methods known in the art. The analysis was done on tissue samples obtained from patients with lung cancer where both tumor and cytologically normal samples were obtained from each patient." (Lal Declaration, ¶ 7.)

As explained by Dr. Lal, "I consider significant differential expression (i.e., altered from normal) for the transcript encoding SEQ ID NO:19 in duplicate lung experiments to occur at Cy5/Cy3 ratios greater than 1.5. As can be seen in Exhibit D, this value was exceeded for 26 out of 36 hybridizations (72%) for 18 different sets of matched normal/tumor tissue samples. Based on these data, it is my opinion that the transcripts for HRM-19 were significantly up-regulated in lung cancer tissue making HRM-19 and the cDNA encoding it very useful in detecting differential expression in lung tumor tissue." (Lal Declaration, ¶ 8.)

The Examiner asserts in response that the utility of SEQ ID NO:19 in diagnosis of lung cancer is allegedly not asserted in the specification as filed (Final Office Action, page 12). Appellants respectfully direct the Examiner's attention to the specification at, for example, p. 18, lines 27-28, wherein the specification discloses that sequences encoding HRM-19 are found in cDNA libraries associated with cell proliferation and cancer. The specification further states that polynucleotides encoding HRM may be used for the diagnosis of cancers, including cancers of the lung (specification, p. 47, lines 24-28). The use of polynucleotides encoding HRM to detect cancer, and the association of increased amounts of transcript with cancer is further disclosed in the specification at, for example, p. 48, lines 7-16, and p. 48, line 29 through p. 49, line 1. The fact that the specification refers to HRMs in general and not HRM-19 in these instances is not relevant, because as discussed in greater detail above, an invention need not have a unique utility to be useful.

Appellants also note that the microarray methods employed by Dr. Lal, in addition to being well known in the art, are also disclosed in the specification in the prophetic example at page 57, lines 1-17 as well as at page 49, line 15 through page 51, line 7. Dr. Lal's results are simply the specific results of

the experiments disclosed as prophetic examples in the specification, and thus were inherently disclosed in the specification as filed.

E. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Final Office Action's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Final Office Action attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities (Final Office Action at page 7). The Final Office Action is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility

The Final Office Action's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, such as the specific substrate it carries, the claimed invention's utility is not sufficiently specific (Final Office Action, page 8). According to the Final Office Action, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Final Office Action would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Final Office Action would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO

guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Final Office Action has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Final Office Action should have looked first to the benefits it is alleged to provide.

B. Membership in a class of useful products can be proof of utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the mitochondrial carrier protein family, the Final Office Action refused to impute the utility of the members of the mitochondrial carrier protein family to HRM-19. In the Final Office Action, the Patent Examiner takes the position that, unless Appellants can identify which particular biological function within the class of mitochondrial carrier proteins is possessed by HRM-19, such as the specific substrate for the carrier, utility cannot be imputed (Final Office Action, pages 8, 11). The Final Office Action also makes much of the Yu article's disclosure that HRM-19 does not have the same function, uncoupling behavior, as some other known mitochondrial carrier proteins (Final Office Action, pages 11-12). To demonstrate utility by membership in the class of mitochondrial carrier proteins, the Examiner in effect would require that all mitochondrial carrier proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long

as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Final Office Action addresses HRM-19 as if the general class in which it is included is not the mitochondrial carrier protein family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the mitochondrial carrier protein family does not. The mitochondrial carrier protein family is sufficiently specific to rule out any reasonable possibility that HRM-19 would not also be useful like the other members of the family.

Because the Final Office Action has not presented any evidence that the mitochondrial carrier class of transporter proteins has any, let alone a substantial number, of useless members, the Final Office Action must conclude that there is a "substantial likelihood" that the HRM-19 encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotides encoding HRM-19 also are useful.

Even if the Final Office Action's "common utility" criterion were correct – and it is not – the mitochondrial carrier protein family would meet it. It is undisputed that known members of the mitochondrial carrier protein family are transporter proteins that transport ions and charged metabolites between the cytosol and the mitochondrial matrix. In fact, the Yu article agrees with Appellants that the HRM-19 is a mitochondrial carrier with a probable role in supporting the enhanced ion and metabolic

flux inherent to thermogenic brown adipose tissue (Yu, page 374, col. 2). A person of ordinary skill in the art need not know any more about how the claimed invention functions in transport between the cytosol and the mitochondrial matrix to use it, and the Final Office Action presents no evidence to the contrary. Instead, the Final Office Action makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given mitochondrial carrier protein transports a specific substrate. The Final Office Action then goes on to assume that the only use for HRM-19 absent knowledge as to how the mitochondrial carrier protein actually works is further study of HRM-19 itself.

Not so. As demonstrated by Appellants, knowledge that HRM-19 is a mitochondrial carrier protein is more than sufficient to make it useful for the diagnosis and treatment of cell proliferative disorders. Indeed, HRM-19 has been shown to be expressed in cancer cells (specification, p. 18, line 28), and the Lal Declaration demonstrates that polynucleotides encoding HRM-19 are overexpressed in lung tumor tissues. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. Because the uses of polynucleotides encoding HRM-19 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

The PTO's rejection of the claims at issue is tantamount to an assertion that the use of an invention as a tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified

utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential toxins and drug candidates that may be targeted to **other** genes or proteins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include use of the claimed polynucleotides in disease diagnosis (specification, pages 47-49), expression profiling and monitoring the activities of therapeutic agents (specification, pages 49-51), and genomic mapping (specification, pages 51-52).

D. The Final Office Action failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

In response to Appellants' identification of HRM-19 as a mitochondrial transport protein, the Examiner has asserted that it is allegedly "nearly impossible from sequence homology alone to attribute a specific and substantial function for the protein" (Office Action mailed September 12, 2002, page 3). The Examiner has further asserted in response to the acknowledged 35% amino acid identity between HRM-19 and the C. elegans putative mitochondrial carrier C16C10 that "[i]n most cases, such degree of homology does not allow the prediction of specific function" (Office Action mailed September 12, 2002, page 7). Appellants respectfully note that the Examiner has provided **no evidence** for this assertion.

Appellants further note that the Brenner reference discloses that the probability that two unrelated polypeptides share more than 30% sequence homology over 150 amino acid residues is exceedingly small. (Brenner, p. 6076). Given homology in excess of 30% over many more than 150 amino acid residues, the probability that the HRM-19 polypeptide encoded for by the claimed polynucleotide is related to the *C. elegans* mitochondrial carrier protein is, accordingly, very high. Thus the known art indicates that the acknowledged homology between HRM-19 and the *C. elegans* mitochondrial carrier protein would in fact be expected to indicate a related function for the two proteins.

The Examiner has also stated that additional data to support a specific function "would include the number of the specific domains associated with said function, and location of highly conserved charge-pairs" (Office Action mailed September 12, 2002, page 3). Appellants disclosed in the specification on page 18, lines 26-27, that the amino acid sequence of HRM-19, has a specific motif characteristic of a mitochondrial carrier protein. Furthermore, as shown in the Declaration of Preeti Lal, submitted September 3, 2002, the HRM-19 protein structure indicates the presence of four mitochondrial carrier domains, six potential transmembrane spanning regions, a likely mitochondrial localization domain, and three regions with reasonable homology to putative mitochondrial energy-transfer signature motifs present in known uncoupling protein functional family members. Therefore, the Lal Declaration and the references attached with the Lal Declaration provide evidentiary support that

one skilled in the art would more likely than not concur with Appellants' asserted functional characterization of HRM-19 as a mitochondrial carrier protein.

The Examiner asserts that the specification did not assert that HRM-19 is a mitochondrial carrier protein but only that it has one mitochondrial carrier motif which "does not necessarily render the protein a mitochondrial carrier (Office Action mailed September 12, 2002, page 7), and that the *C. elegans* homolog is only a "putative" carrier. Both facts taken together, however, would lead one of skill in the art to believe that HRM-19 is in fact a mitochondrial carrier, a fact reinforced by the Lal Declaration. New post-filing evidence provided in the Lal Declaration, such as the Yu article which provides experimental evidence that HRM-19 is a mitochondrial carrier protein, serve to **confirm** what was previously asserted.

The Lal Declaration also demonstrated that the transcripts for HRM-19 were significantly, differentially, up-regulated (overexpressed) in lung tissue samples from cancer patients as compared to matched normal samples from the same patient. Therefore, HRM-19, and the cDNA encoding it, are of diagnostic use in detecting lung cancers.

The Final Office Action asserts in response that the utility of SEQ ID NO:19 in diagnosis of lung cancer is allegedly not asserted in the specification as filed (Final Office Action, page 12). Appellants respectfully direct the Board's attention to the specification at, for example, page 18, lines 27-28, wherein the specification discloses that sequences encoding HRM-19 are found in cDNA libraries associated with cell proliferation and cancer. The specification further states that polynucleotides encoding HRM may be used for the diagnosis of cancers, including cancers of the lung (specification, page 47, lines 24-28). The use of polynucleotides encoding HRM to detect cancer, and the association of increased amounts of transcript with cancer is further disclosed in the specification at, for example, page 48, lines 7-16, and page 48, line 29 through page 49, line 1. The fact that the specification refers to HRMs in general and not HRM-19 in these instances is not relevant, because as discussed in greater detail above, an invention need not have a unique utility to be useful.

Appellants also note that the microarray methods employed by Dr. Lal, in addition to being well known in the art, are also disclosed in the specification in the prophetic example at page 57, lines 1-17 as well as at page 49, line 15 through page 51, line 7. Dr. Lal's results are simply the specific results of

the experiments disclosed as prophetic examples in the specification, and thus were inherently disclosed in the specification as filed.

Furthermore, as discussed in the Bedilion declaration, pre-September 1997 articles known in the art at the time of filing of the Lal '750 specification point to the role of mitochondrial carrier proteins, such as HRM-19, in cell proliferative disorders (Bedilion Declaration, ¶ 15(f)). Thus, one of ordinary skill in the art would reasonably expect polynucleotides encoding HRM-19 to be useful in the diagnosis of cancers, including lung cancer.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82

J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax," to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specification as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-

established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,

INCYTE CORPORATION

Date: August 4, 2003

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APPENDIX - CLAIMS ON APPEAL

2. An isolated polynucleotide comprising a nucleic acid sequence encoding a protein having the amino acid sequence of SEQ ID NO:19 or the complete complement of the polynucleotide.

3. A composition comprising the polynucleotide of claim 2 and a reporter molecule.

4. An isolated polynucleotide consisting of the nucleic acid sequence of SEQ ID NO:68 or the complete complement of the polynucleotide.

5. A vector containing the polynucleotide of claim 2.

6. A host cell containing the vector of claim 5.

7. A method for using a polynucleotide to produce a protein comprising:

a) culturing the host cell of claim 6 under conditions for the expression of the protein; and

b) recovering the protein from the host cell culture.

8. A method for using a polynucleotide to detect expression of a nucleic acid in a sample, the method comprising:

a) hybridizing the polynucleotide of claim 2 to nucleic acids of the sample, thereby forming a hybridization complex; and

b) detecting hybridization complex formation, wherein complex formation indicates the expression of the polynucleotide in the sample.

9. The method of claim 8 wherein the polynucleotide is attached to a substrate or bonded to the surface of a microarray.

10. The method of claim 8 wherein the nucleic acids of the sample are amplified prior to hybridization.

11. A method of using a polynucleotide to screen a plurality of molecules to identify a ligand, the method comprising:

a) combining the polynucleotide of claim 2 with a plurality of molecules under conditions to allow specific binding; and

b) detecting specific binding, thereby identifying a ligand which specifically binds the polynucleotide.

12. The method of claim 11 wherein the molecules are selected from DNA molecules, RNA molecules, peptide nucleic acids, artificial chromosome constructions, peptides, and transcription factors.

13. A method for diagnosing a disease associated with gene expression in a sample containing nucleic acids, the method comprising:

a) hybridizing a polynucleotide of claim 2 to nucleic acids of the sample under conditions to form a hybridization complex,

b) comparing hybridization complex formation with standards, thereby diagnosing the disease.

14. The method of claim 13 wherein expression is diagnostic of lung cancer.

21. The method of claim 13 wherein the sample is from lung.